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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,928	WARD ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *47-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-15,28-31 and 44-46* is/are rejected.

7)☒ Claim(s) *3,5-11,14,16-27,30 and 32-43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/08 and 10/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the preliminary amendment filed on 14 April 2009 and the election filed on 15 September 2009.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-46, and SEQ ID NO:7, in the reply filed on 15 September 2009 is acknowledged. The traversal is on the grounds that Applicants should be given the opportunity to argue the merits during prosecution and that there is no disclosure or suggestion of using the vector recited in the present claims in conjunction with interrupted antiretroviral drug therapy to delay viral rebound.

Applicants' traversal to the restriction is acknowledged, however, not persuasive. Contrary to Applicants' argument, the claimed invention does not provide a contribution over the prior art as previously set forth in the Lack of Unity requirement mailed 15 June 2009 and in the rejection set forth below. Thus, the claimed invention cannot be said to have unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-62 are pending. Claims 47-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 September 2009.

Claims 1-46 are currently examined.

Information Disclosure Statement

Applicant's Information Disclosure Statements (IDS) filed 12 February 2008 and 26 October 2006 have each been received and entered into the application. As reflected by the attached, signed copies of form PTO-1449A, the Examiner has considered the cited references.

Specification

The abstract of the disclosure is objected to because there is legal phraseology (i.e. the word "said" in the fifth line) in the text. Correction is required. See MPEP § 608.01(b).

Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 45 and paragraph [0161], for example.

The disclosure is objected to because of the following informalities: the phrase "a number of different of mechanisms" in the paragraph [0052] is grammatically or idiomatically incorrect.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Poxvirus vector encoding retrovirus antigen(s) and cytokine.

Appropriate correction is required.

Claim Objections

Claims 5-11, 16-27 and 32-43 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). For example, claim 5 is multiply dependent on claim 1, 2, 3 or 4 while claims 3 and 4 are both multiply dependent on claim 1 or 2. Accordingly, the claims have not been further treated on the merits.

Claims 3, 14 and 30 are objected to because of the following informalities: the phrase "retroviral viral" in the claim limitation is redundant. Appropriate correction is required.

Double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 12-15, and 28-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 7,276,242 B1 in view of Rosenwirth *et al.* (1999).

The instant claim 1 is drawn to a method of reducing or alleviating one or more side effects of anti-retroviral drug therapy comprising administering to a subject a poxvirus vector encoding:

(a) a retrovirus antigen;

(b) the retrovirus antigen and a cytokine; or

(c) a functional homolog, derivative, part or analog of the retrovirus antigen and/or cytokine,

in conjunction with interrupted anti-retroviral drug therapy wherein (a) the antigen, or (b) the antigen and the cytokine, are expressed in the subject.

Claims 12 and 28 narrow down the limitation of poxvirus encoding proteins to the retrovirus antigen and a cytokine, or a functional homolog, derivative, part or analog of the retrovirus antigen and/or cytokine. Claim 13 further limits the retrovirus antigen to HIV antigen. Claims 4 and 29 further limit the retroviral infection to HIV infection. Claims 3, 14 and 30 further limit the subject to one exhibiting a low retroviral load after anti-retroviral

therapy whereas claims 4, 15 and 31 further limit the subject to one exhibiting a low retroviral load before anti-retroviral therapy.

Claim 3 of Patent No. 7,276,242 B1 recites a species method of inducing, enhancing or otherwise stimulating, in a mammal, an immune response to HIV comprising administering a recombinant viral construct comprising a fowlpox virus vector or functional derivative thereof encoding HIV Gag and/or Pol or derivatives thereof and gamma-interferon or a functional derivative thereof.

The HIV as recited in the patent claim 3 is a species of the retrovirus as recited in the instant claims 1, 2, 4, 12, 14, 15, 28, 30 and 31. The patent claim differs from all the instant claims in that it does not specifically recite "in conjunction with interrupted anti-retroviral drug therapy.

However, Rosenwirth *et al.* discloses therapeutic vaccination in conjunction with stopped or interrupted anti-retroviral drug therapy (page 196, left column, first partial paragraph) and provides the motivation that reduction of viral load by drug treatment is expected to allow the immune system to recover and to respond appropriately to a vaccine, so that the induced immune response may be capable of suppressing virus replication to such an extent that low steady-state levels of virus load can be maintained after treatment is stopped. In particular, rhesus macaques chronically infected with SHIV were treated with a potent chemical anti-HIV drug (PMPA, reference is made to HAART on page 196) and when the virus load had decreased significantly (below 1000 RNA copies per ml plasma, figure 1 and page 198), the animals were immunized with SIV genes *env, gag/pol, rev, tat and nef*

inserted in different expression vector systems (modified vaccinia virus ankara, MVA, and semliki forest virus, SFV; page 196). Rosenwirth *et al.* explicitly suggests that the motivation to add the immunization therapy with a poxvirus vector such as MVA expressing HIV genes after the drug treatment is to stimulate an efficient immune response during the period of low virus load and restored $CD4^+$ cell levels, which might be capable of keeping the virus under long-lasting control after treatment is stopped, in order to shorten the time span of drug treatment to avoid the side effects of the emergence of multiple drug-resistant mutants and toxicity. See Abstract.

While HIV is a retrovirus that infects humans, SIV is the simian species of a retrovirus that infects monkeys and shares similarity in structural proteins with HIV. Therefore, it would have been obvious to modify the method of claim 3 of U.S. Patent No. 7,276,242 B1 such that the immunization with a fowlpox vector expressing HIV Gag and/or Pol or derivatives thereof and gamma-interferon or functional derivative thereof is used in a subject in conjunction with a stopped anti-retroviral drug treatment, i.e. after the anti-retroviral therapy or before a second round of anti-retroviral therapy. One having ordinary skill in the art would have been motivated to make such a modification to stimulate an efficient immune response during the period of low virus load and restored $CD4^+$ cell levels, which might be capable of keeping the virus under long-lasting control after treatment is stopped, in order to shorten the time span of drug treatment to avoid the side effects of the emergence of multiple drug-resistant mutants and toxicity, as per the teachings of Rosenwirth *et al.*

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 12-15, 28-31 and 44-46 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "retroviral infection" in the first line. There is insufficient antecedent basis for this limitation in the claim because the base claim 1 does not recite infection.

The term "low retroviral load" in claims 1, 3, 4, 12, 14, 15, 30 and 31 is a relative term which renders the claim indefinite. The term "low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term is vague and confusing because it does not readily manifest the metes and bounds of the claimed invention. Applicants should clearly and unambiguously identify the salient characteristics associated with the term, "low retroviral load," such as the number of viral copies per ml of blood serum.

Regarding claims 1, 12 and 28, the phrase "reducing or alleviating one or more side effects of anti-retroviral drug therapy" in the preamble is also vague because it is unclear how the side effects reduction is related to the result of preventing, reducing or delaying viral

rebound during interruption of anti-retroviral drug treatment. In other words, it is confusing how the reduction of viral rebound ties in with the preamble of reducing or alleviating the existent side effects of anti-retroviral drug therapy.

Well-documented side effects associated with the administration of anti-retroviral therapy include, inter alia, nausea, severe neutropenia, myelosuppression, peripheral neurotoxicity, CNS toxicity, hyperlipidemia, and diabetes mellitus. However, it is not readily manifest how the administration of a poxvirus vector encoding a retroviral antigen will reduce or alleviate any of these side-effects.

Applicants may obviate the rejection by amending claims 1, 12 and 28 as follows: replace the phrase "reducing or alleviating one or more side effects of anti-retroviral drug therapy," in the preamble with the phrase "reducing or delaying viral rebound during interruption of anti-retroviral drug treatment".

Claims 2-4, 13-15, 29-31 are rejected for depending from an indefinite base claim.

Claims 44-46 provide for the use of a recombinant vector, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. For example, it is unclear whether Applicants are intended to claim a method of making a composition comprising the recited recombinant vector, a treatment/immunization method of administering the recombinant vector, a prophylaxis method of administering the

recombinant vector, or a protein expression method of transfecting cells with the recombinant vector.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 44-46 are rejected under 35 U.S.C. §101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 44 is drawn to a use of a recombinant vector comprising a sequence of nucleotides encoding a retrovirus antigen or a functional derivative, homolog, part or analog thereof, and a sequence of nucleotides encoding a cytokine or a functional derivative, homolog, part or analog thereof in the manufacture of a medicament for use in conjunction with interrupted anti-retroviral drug treatment in maintaining or prolonging a low retroviral load in a subject for a period of time, and in preventing, reducing or delaying viral rebound during interruption of anti-retroviral drug treatment.

Claim 45 is drawn to a use of a recombinant vector comprising a sequence of nucleotides encoding retrovirus antigen or a functional derivative, homolog, pan or analog

thereof, and a sequence of nucleotides encoding a cytokine or a functional derivative, homolog, part or analog thereof, in the manufacture of a medicament for use in reducing or alleviating one or more side effects of anti-retroviral drug therapy.

Claim 46 is drawn a use according to claim 44 or 45, wherein the retrovirus is HIV.

Claims 44-46 do not set forth any active method step and thus are not proper process claims.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

Claims 1-4, 12-15 and 28-31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-4, 12-15 and 28-31 are broadly drawn to an immunization method employing a vast genus of functional homologs, derivatives, part or analogs of the retrovirus antigens and/or the cytokines that are required to maintain or prolong a low retroviral load in a subject. The functional effect encompassed by the claims includes cytotoxic lymphocytes

(CTL), neutralizing antibodies, or humoral antibodies that can recognize and bind any homologs, derivatives, parts or analogs derived from the retrovirus antigen, which effect is also enhanced by the presence of any homologs, derivatives, parts or analogs derived from a cytokine.

The written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings or structural chemical formulas, or by disclosure of relevant, identifying characteristics, *i.e.*, complete/partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, by predictability in the art, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, a "functional homolog, derivative, part or analog" is not adequately described because the specification only identifies the desired result of "maintaining or prolonging a low retroviral load in the subject for a period of time and effective in preventing, reducing or delaying viral rebound during interruption of anti-retroviral drug treatment." The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus to which the claims are drawn, such as the nature of the induction of immune responses; the structure of the epitopes; what modifications could be made to the antigens and cytokines; how the homologs, derivatives, parts or analogs can be derived; what constitutes a derivative; or what constitutes an analog, so that the skilled artisan could immediately envision, or recognize at

least a substantial number of members of the claimed genus. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the retrovirus or HIV antigen homolog, derivative, part or analog, or which amino acids might be replaced so that the resultant structure retains the activity of its parent (i.e. to bind to a given antigen-presenting cell so as to induce an immune response). There is not even a single representative species disclosed in the specification. There is no discussion of which regions of the retrovirus antigen and cytokine can be mutated (i.e. deleted, inserted, substituted) or chemically modified to retain their respective antigenic and adjuvant activity. Therefore the specification fails to adequately describe at least a substantial number of members of the genus to which the claims are based.

Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." M.P.E.P. § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of "functional homolog, derivative, part or analog". Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of "functional homolog, derivative, part or analog."

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state,

"[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.*

recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the epitopes that can bind a given binding agent can only be identified empirically. Absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of binding agents, epitopes, mimotopes, and antibody fragments, the skilled artisan could not immediately recognize or distinguish members of the claimed genus. Therefore, because the art is unpredictable, in accordance with the Guidelines, the description is not deemed representative of the genus of homologs, derivatives, parts or analogs of the retrovirus antigen and cytokine.

Therefore, claims 1-4, 12-15 and 28-31 do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115).

Scope of Enablement Rejection

Claims 1-4 and 12-15 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing or delaying viral rebound during interruption

of anti-retroviral drug treatment by administering a poxvirus vector encoding a retrovirus antigen and/or cytokine, does not reasonably provide enablement for preventing viral rebound during interruption of anti-retroviral drug treatment, or for reducing or delaying viral rebound by administering a poxvirus vector encoding a homolog, analog, part or derivative of a retrovirus antigen and/or cytokine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention: The claims are directed to a method of preventing viral rebound with a recombinant poxvirus-based retrovirus- or HIV-vaccine.

Breadth of the claims: The claims encompass preventing the replication of any retrovirus strain or subtype. The claims are not limited to administering the poxvirus vector

comprising a single nucleic acid sequence, encompassing the expression of a wide variety of sequences encoding uncharacterized homolog, derivative, part or analog of the retrovirus antigen and/or the cytokine as discussed above.

Amount of direction or guidance presented: The disclosure fails to provide adequate guidance pertaining to the correlates of protective immunity in human. Specifically, the disclosure does not elucidate the following critical factors of an effective vaccine: (1) the specificity and titer of the immune response required for protection; (2) the presence of a neutralizing antibody (Nab) response, a cytotoxic T lymphocyte (CTL) response, or both; (3) the molecular determinants (i.e., Nab epitopes; CTL epitopes) that are responsible for the desired immune response; (4) the length of the immune response has to be long term; and (5) the most effective means for presenting said determinants? The disclosure fails to provide adequate guidance demonstrating that retrovirus or HIV-1 antigens can be induced and expressed at a level that will lead to a long-term protective or therapeutic immune response so as to prevent viral rebound. The claimed invention is based upon the assertion that the expression ofa retroviral gene, or its homolog, derivative, part or analog thereof, can be induced by the addition of a cytokine, or its homolog, derivative, part or analog thereof. However, the disclosure fails to provide any guidance pertaining to the level of expression required for any particular retrovirus antigen that results in the desired immune response preventing retroviral rebound. Thus, it is not manifest from the disclosure that the claimed poxvirus vector can express the retroviral antigen at a sufficient level and for a sufficient period of time to induce the desired response.

Presence or absence of working examples: The disclosure fails to provide any working embodiments. While there appears to be some preliminary data in the specification showing reduction in the HIV viral load and therapeutic effect, this does not constitute a proper working embodiment because the viral reduction data presented is not equivalent to viral rebound prevention. Even though the viral rebound is reduced in patients, there is still a low amount of viral replication, which leads to a lower extent of viral rebound.

The state of the prior art: It is well known in the art that retroviral infections, in general, and HIV infections, in particular, are refractory to anti-viral therapies (Onafuwa-Nuga, 2009). The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation, despite the high level of skill in the art. It is

well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion because HIV have evolved a way to circumvent the bivalent effect that is key to the potency of antibodies by spreading its envelope spikes so far apart that the antibodies simply don't have a long enough reach to effectively neutralized the viruses they are meant to target (Klein *et al.*, 2009).

Letvin *et al.* (1998, Science, Vol. 280, p. 1875-1880) stated: "HIV is a uniquely difficult target for vaccine development. Immune correlates of protective immunity against HIV-1 infection remain uncertain." The Letvin group further indicated that such difficulty for HIV vaccine development comes from the unique property of the HIV virus, including persistent replication in the infected individual, rapid mutation during infection, persist indefinitely as latent proviral DNA and mucosal route of transmission (see page 1875, 1st col., 2nd ¶). Such property is prevalent among all retroviruses. Burton *et al.* (1998, Nature Medicine, Vol 4, p. 495-498) also addressed several reasons for difficulty in generating an effective HIV vaccine. Burton *et al.* proposes that the most important distinguishing features of HIV are the nature of the virus envelope and the ability of a retrovirus to integrate into host DNA, which render it extremely difficult to present the envelope glycoproteins in a way that stimulates a significant antibody response or memory or illicit cellular immune response (see p. 496, 2nd col., 3rd ¶). Another obstacle in developing an effective HIV vaccine is the lack of an animal model that is predictive of the outcomes in human subjects. Feinberg *et al.* (2002, Nature Medicine, Vol. 8, p. 207-210) state: "rhesus

macaque model are by far the most widely used because it can be infected with various simian immunodeficiency virus strains of differing virulence and develop simian AIDS. However, because HIV-1 does not productively infect macaques, it cannot be used as a challenge virus to assess whether a given vaccine can prevent or ameliorate infection. Hence, preclinical AIDS vaccine models rarely test the identical vaccine constructs that are planned for human use." Although chimeric virus SHIV were engineered to increase the relevance of the macaque model to human vaccine trials, such "virus of choice," SHIV-89.6, for example, still differs in important ways from the HIV-1 strains that most commonly infect and are transmitted between humans (see page 207, 1st col., 2nd ¶). In view of the teaching from the prior art, HIV vaccine does not exist at the time of filing. The specification neither teaches how to overcome the obstacles existing in the art or how to use the claimed method of administering a poxvirus-based retroviral or HIV vaccine to prevent viral rebound. As such, the disclosure does not support the claimed method.

Relative skill of those in the art: the relative skill of those in the art is high due to so many unknown aspects of retroviral or HIV infection in human patients and the aforementioned uncertainties about the effect of the vaccine vectors in human trials.

Predictability or unpredictability of the art: The state of the art vis-à-vis the development of HIV or retroviral vaccines is highly unpredictable and has been characterized by repeated failure due to a number of factors: (1) Key biological factors that lead to high recombination rates for all retroviruses are the recombination-prone nature of their reverse transcription machinery and their pseudodiploid RNA genomes. However, HIV-

1 genes recombine even more frequently than do those of many other retroviruses (Onafuwa-Nuga, 2009). An initially benign viral mutant can give rise to virulent progeny with unpredictable genotypes (Whitney, 2004). Efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations. The main problem with HIV therapeutics and vaccines is that there has not been a solution to overcome the enormous sequence heterogeneity within the ever-changing chameleon-like genome of HIV-1 (Altman & Feinberg, 2004; Desrosiers, 2004). (2) The complexities of HIV-1 pathogenesis, the high mutation rate of the viral genome, and its ability to persist in lymphoid and other tissues, all allow HIV-1 to evade many therapies (Yee, 2001). (3) Such genetic variation will make it extremely difficult to generate cross-neutralizing HIV immune responses. The genetic variability of the viral envelope proteins allows the virus to escape neutralizing antibodies and underlines the difficulty in identifying immunogens and immunization platforms that consistently induce antibodies that can neutralize several HIV clades (Phogat, 2007). (4) Successful, well-tested vaccines all elicit broad integrated responses that encompass all effector arms of immune response, including innate (Toll-like receptor-mediated) responses, NK cell responses, and Th1/Th2 response. There is uncertainty about whether these recombinant virus vectors can induce long-lasting, broad, and protective immune responses. A recombinant canarypox vaccine delivered with a recombinant HIV envelope protein shows disappointing immunogenicity in human trials (Letvin, 2005). Recombinant poxvirus boosting of DNA-primed rhesus monkeys augments peak but not memory T lymphocyte responses (Santra, 2004). Information is currently

lacking on the innate responses elicited by the different vectors, including adenovirus and poxvirus early after immunication and in ex vivo systems (Sekaly, 2008). (5) It remains unclear whether there is a general danger of using recombinant viral vectors to immunize against HIV, including preexisting vector-specific immunity (whether innate or adaptive) that prevents the full development of an HIV-specific immune response. The vector-specific immune response and the immunomodulatory function of vector-encoded proteins could compete or bias HIV-specific responses (Sekaly, 2008). (6) Current immune-monitoring strategies are focused on measuring effector T cell response. They do not, however, measure memory and its renewal or persistence. Nor do they allow us to evaluate the homing of T cells to mucosal sites, the primary site of HIV infection. The field is still lacking assays that will help in predicting the development of protective immunity in response to vaccines (Sekaly, 2008). (7) Further complicating the issue is the possibility that HIV and the recombinant poxvirus could mutate around each other and recombine to make an altogether new virus, which can facilitate drug resistance and may allow superinfecting HIV-1 strains to evade preexisting immune responses (Onafuwa-Nuga, 2009).

Quantity of experimentation necessary: The obstacles for developing a HIV vaccine effective in human is discussed above. The skilled artisan does not consider that data from macaque model is predictive of successful outcome in human trial (see Feinberg *et al*). Therefore, one skilled in the art would have to rely solely on the guidance provided in the specification for using claimed invention to elicit a protective immune response. However, the specification does not provide any guidance on how to overcome the art recognized

obstacles in developing a vector vaccine against HIV or any retrovirus. Neither does the specification demonstrate that the claimed vector is effective as a retroviral or HIV vaccine for preventing viral rebound in humans. Moreover, the broad claims are drawn to a vector that expresses a functional homolog, derivative, part or analog of a retrovirus antigen and/or a cytokine, and there is no evidence that the homolog, derivative, part or analog itself is sufficient to elicit any immune response for viral rebound prevention. Therefore, one skilled in the art would have to engage in undue experimentation to use the claimed vector to prevent viral rebound. Thus, the claimed invention is not enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.* (WO 01/54701 A1).

The instant claims are directed to a method comprising administering to a subject a poxvirus vector encoding an antigen of the retrovirus, a functional homolog, part, derivative or analog thereof, in conjunction with interrupted anti-retroviral drug therapy.

Ho *et al.* teaches a method of permitting cessation of antiviral therapy on HIV-infected subjects, who have a viral load of less than 5,000 viral copies per ml of plasma

(limitation in claims 3 and 4) and a $CD4^+$ T-cell count of above 500 cells/ml, and who have been treated with a potent combination of antiviral agents that contributed to a lower viral copy number and equal or higher $CD4^+$ T-cell count than before treatment, without virus rebound or with at least a delayed virus rebound or a decreased post-rebound viral load, by inducing both humoral and cell-mediated immunity and achieving an immunological control of persistent infectious virus after discontinuation of antiviral therapy (page 2, lines 15-34). The method comprises inducing HIV-specific (limitation in claim 2) immune responses by administering an attenuated recombinant poxvirus (limitation in claim 1) that includes [one] or more nucleic acids encoding one or more HIV-specific immunogens (page 3, lines 2-5). Thus the reference discloses each and every claim limitation and is clearly anticipatory.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-15 and 28-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* (WO 01/54701) in view of Kent *et al.* (WO 00/28003, cited in IDS filed 26 October 2006).

Claims 12 and 28 are directed to a method comprising administering to a subject a poxvirus vector encoding a retrovirus antigen and a cytokine, or a functional homolog, part,

derivative or analog, in conjunction with interrupted anti-retroviral drug therapy. Claim 13 further limits the retrovirus antigen to HIV antigen. Claim 29 further limits the retroviral infection to HIV infection. Claims 14 and 30 further limit the subject to one exhibiting a low retroviral load after anti-retroviral therapy whereas claims 15 and 31 further limit the subject to one exhibiting a low retroviral load before anti-retroviral therapy.

Ho *et al.* discloses a method of permitting cessation of antiviral therapy on HIV-infected subjects, who have a viral load of less than 5,000 viral copies per ml of plasma and a $CD4^+$ T-cell count of above 500 cells/ml, and who have been treated with a potent combination of antiviral agents that contributed to a lower viral copy number and equal or higher $CD4^+$ T-cell count than before treatment, without virus rebound or with at least a delayed virus rebound or a decreased post-rebound viral load, by inducing both humoral and cell-mediated immunity and achieving an immunological control of persistent infectious virus after discontinuation of antiviral therapy (page 2, lines 15-34). The method comprises inducing HIV-specific immune responses by administering an attenuated recombinant poxvirus that includes [one] or more nucleic acids encoding one or more HIV-specific immunogens (page 3, lines 2-5), which reads on to every limitation of the claimed invention.

Ho *et al.* does not disclose co-expressing a cytokine with an HIV antigen in the poxvirus vector, although Ho *et al.* specifically suggests combining an HIV antigen with an immunostimulatory or co-stimulatory molecules such as interleukin 2, which is a cytokine (page 3, lines 6-9).

Kent *et al.* discloses a poxvirus vector encoding HIV-1 Gag and/or Pol or derivatives thereof and interferon-gamma or a functional derivative thereof that is effective in inducing, enhancing or otherwise stimulating an immune response to HIV Gag and/or Pol. See page 3, lines 15-31.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Ho *et al.* so as to replace the poxvirus vector with the fowlpox vector encoding HIV-1 Gag and/or Pol or derivatives thereof and interferon-gamma or a functional derivative thereof as taught by Kent *et al.* One having ordinary skill in the art would have been motivated to make such a modification to enhance the HIV-specific immune responses by additionally expressing interferon-gamma as taught by Kent *et al.* (page 28, lines 4-14). There would have been a reasonable expectation of success, given the effectiveness of the fowlpox vector encoding HIV-1 Gag and/or Pol and interferon-gamma in inducing, enhancing or otherwise stimulating an immune response to HIV Gag and/or Pol, as taught by Kent *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the application as filed so as not to add new matter. See MPEP §714.02 and §2163.06.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louise Humphrey, Ph.D./
Examiner, Art Unit 1648

2 December 2009